Summary - Too Hot, Too Cold, Too High, Too Low - Blame it on Dysautonomia!

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Introduction Dr. Boles is a clinician and researcher dedicated to further discovery of treatments which will offer a better quality of life and a decrease in symptoms for children and adults suffering from mitochondrial functional disorders such as autism, cyclic vomiting syndrome and depression. The application of science and research for his patients is apparent in his role a Director of the Metabolic and Mitochondrial Disorders Clinic at Children's Hospital of Los Angeles and director of a research laboratory in mitochondrial genomics as well as his leadership within organizations like CureMito.org.

His discussion focuses on the disturbing symptoms of dysautonomia, which, although usually not life-threatening, affect a person's daily quality of life in a profound manner. Dysautonomia describes an inability of the autonomic nervous system to regulate "typical" or "automatic" body functions, thus causing troubling symptoms like heat intolerance, erratic blood pressure, dizziness, nausea, and intermittent GI dysfunction. Dr. Boles is one of the few physicians specializing in functional disorders as they relate to mitochondrial disease.

Dysautonomia The first few slides show the complex of symptoms that may be the result of dysautonomia. The first slide demonstrates the "pedigree" or matrilineal inheritance of many functional disorders in one particular family. The elephant slide also shows the many related functional mitochondrial disorders, such as cyclic vomiting syndrome (CVS) and migraines can be related to dysautonomia.

The autonomic nervous system (ANS) is that part of the nervous system which reacts to danger. It is alert and signals the body to "run away quickly," and it turns on various body systems immediately when it senses danger, high stress or crisis. When the danger has passed, it then gives the body the "all clear signal." The **sympathetic nervous system** is that part of the autonomic system which switches on for danger, and it reacts very quickly. The **parasympathetic nervous system** is the "off switch" and signals the body that the crisis is over and all can go back to normal. The slides demonstrate how all encompassing the autonomic system is; virtually every organ is innervated by an autonomic nerve. The sympathetic nerves come out mainly from the spinal area; they are fairly short and close to the organs they stimulate (a few inches in length). When they switch on, they do so quickly and the entire system is "on." The parasympathetic nerves, on the other hand, come out mainly from the brain (though a few do come out from the bottom of the spine) and travel much longer distances to the organs which they stimulate (several yards); they are quite slow to react and it takes a much longer time for the body's systems to "turn off." Typically, for people with mitochondrial disease, the sympathetic system works well, whereas the parasympathetic system does not - thus causing the various functional disorders we

see.

Case Study 1 This case study of a 15 year old girl demonstrates this phenomenon. She came to clinic with symptoms of cyclic vomiting syndrome, constipation and chronic fatigue. During vomiting episodes and viral infections, she could not read. Her ophthalmologist could find nothing wrong with her eyesight (including her optic nerves, eye structure, etc.) and her school blamed her symptoms on psychiatric illness. This teenager also preferred to always wear a hat - even indoors.

In truth, her symptoms were related to dysautonomia. When she became ill, her sympathetic system would turn on and thus she had strong peripheral vision (for seeing distances in case of danger her pupils dilated), but her parasympathetic system was very slow to respond and turn off so her eyes could not focus on near things (pupils did not constrict or accommodate for central vision) which is necessary for reading. Bright lights bothered her indoors as well. These symptoms make sense when you consider dysautonomia: her sympathetic system worked, but her parasympathetic system did not because of decreased mitochondrial function. She was in full "on" mode for much longer than necessary every time she became ill or was under stress. She could use reading glasses (even though her eyes were structurally normal), and sunglasses or hats to decrease the glare. Her issues were functional not structural.

Blood Vessels The next few slides show blood vessels, both arteries and veins. Most of the symptoms of dysautonomia come from the reactions of the blood vessels to signals from the sympathetic and parasympathetic nerves. The arteries are depicted in red on the slides and the veins in blue. There are lots of muscles that are controlled by nerves which cause the arteries to constrict or dilate; the veins have fewer muscles. The arteries supply blood to organs so they are important in organ function.

POTS: Postural Orthostatic Tachycardia Syndrome is a condition associated with light headedness, fainting or dizziness when changing positions - especially from sitting or lying to standing. The arteries control the amount of blood going to the brain, and the blood has to travel further when one changes position from lying or sitting to standing. Usually, muscles in the legs and gut would constrict the blood vessels there so that more blood could travel to the brain - and this would be done very quickly. If it does not happen immediately, the individual gets light headed, can even faint, or (more common in adolescents) appears like a seizure. The heart beats faster in an attempt to get more blood pumped to the brain. All of this occurs because the signals to the muscles which in turn control the arteries do not work quite fast enough to adapt to the change.

Other related symptoms which we see with mitochondrial disease include changes in skin color, either redness and flushing or blueness and cold, because the blood vessels cannot react quickly enough to changes in temperature. The body's normal response to cold is to constrict blood vessels in the skin so that we don't lose too much heat. Likewise, when it is hot, the blood vessels dilate so we can lose heat. For many Mito patients, this does not happen quickly enough (the parasympathetic system is not working). Many patients appear to have "mottling", especially on the legs.

Pain syndromes also are related to this phenomenon. Too little blood flow to an area may stimulate pain fibers, while too much blood flow causes more pain (migraines). The body cannot function properly due to this manifestation of dysautonomia.

Case Study 2 A 14-year-old boy with mild dysautonomia symptoms (his sisters had many more symptoms) lost consciousness, preceded by nausea and dizziness. Paramedics were called and he was sent to the ER, then to the ICU. Later they found that he had not actually lost consciousness, he had heard them throughout, but he had been unable to talk during the episode. This was an extreme case of POTS. For unknown reasons, this appears to be more common in adolescents.

Treatment for POTS typically includes increased fluids and salt intake as a first line approach. Obviously, teaching the patient to remember to get up slowly when changing positions is necessary. Medications can be used in extreme cases (L-arginine is generally recommended).

CRPS Complex Regional Pain Syndrome This usually occurs after trauma to tissue or after surgery (any time there is damage to tissue). In this syndrome, the pain does not go away after the trauma, but rather gets worse in intensity. Other abnormal autonomic symptoms also may occur like discolored skin (hotter or colder than normal) and swelling. The slides show an injury to a 16 year old who was unable to walk because of pain until he received treatment. As difficult as it is, exercise and daily use of the affected limbs is a very important treatment. Even though there is significant pain, immobilization is counterproductive and can worsen CRPS. Giving IV fluids at the very onset is also important (10% dextrose with other electrolytes, also known as D-10 with lytes).

Cardiac effects Dysautonomia certainly effects cardiac function. With dysautonomia, patients may have both increased heart rate at times as well as decreased heart rates. Individuals with chest pain need to rule out cardiac causes, although chest pain is most commonly related to **GERD (Gastric Esophogeal Reflux Disease)** . GERD generally causes pain in the morning or when lying down, but does not include feelings of shortness of breath. People with GERD also do not typically have fainting (syncope). Nonetheless, it is important for Mitochondrial disease patients to undergo appropriate cardiac testing (often including an echocardiogram) to rule out structural problems as a cause of these symptoms.

Secretory Glands All the glands in the body are part of the autonomic system; they are told to turn on or off by its signals. Consequently, dysautonomia can show various symptoms. There can be too much sweat or not enough. Dry mouth or drooling might be another typical symptom, or dry eyes and/or too much tearing. In the GI system, diarrhea or constipation are common symptoms.

GI System The GI system seems to be the one most affected by dysautonomia in mitochondrial patients**.** This should not be a surprise since the GI system has high-energy demands and is made up of many muscles, nerves and glands. Since the

sympathetic system tells the GI tract to shut down (no time to eat - crisis is here - danger), digestion more or less stops, thus causing many symptoms common to mito patients. When the parasympathetic system comes on much later, then blood flow to GI tract increases and digestion is now allowed. Common symptoms include dysmotility - which actually means "bad movement" - so the gut is either moving too fast (resulting in diarrhea) or too slow (resulting in bloating and constipation). Dysmotility could occur at any level of the GI system: mouth, esophagus, stomach (delayed gastric emptying), small intestine (malabsorption), large intestine (irritable bowel).

GERD is fairly common in the general population (about 10- 20% of adults), but is almost universal in the Mito population. Clinical signs vary and can include heartburn, chronic nausea, allergies (acid refluxes into nose), asthma (acid refluxes into lungs); additionally, fatigue and lack of growth often occur in children with chronic reflux. The slides which accompany this summary show numerous ways to diagnose GERD as well as some treatments. Among the treatments is to be sure to not lie flat, but rather have head of bed elevated. Prilosec is also found to be an over the counter drug that works. Delayed gastric emptying and gastric paresis are related problems that often affect Mito patients as well.

Recommendations to treat these various GI problems include: eating small amounts of food throughout the day rather than three large meals, a low fat diet is tolerated better, and maintenance fluids (by mouth) throughout the day. Malabsorption can be another problem, but is harder to treat. If the small intestine is where food is absorbed and it is not working, there is not a lot we can do. Diarrhea and failure to thrive are sometimes related to malabsorption.

Irritable Bowel Syndrome (IBS) is a common problem among the general population. Chronic constipation alternating with diarrhea can occur. For Mito patients, the incidence of IBS is even higher than the general public. Clinically, IBS can be complicated to diagnosis when presented as chronic belly pain (with or without chronic diarrhea and constipation). Treatment for IBS often includes a healthy low fat diet and use of osmolytic laxatives (such as Miralax). This medication basically helps draw water into the bowel to prevent constipation. It does, however, cause dehydration, so care must be taken to keep well-hydrated. Miralax should be used by mito patients prophylactically - before constipation sets in. IBS can become serious if there is an obstruction. If vomiting occurs, it should be taken seriously.

SUMMARY: General Principles of Therapy for Mitochondrial Dysautonomia

- Decrease energy demand
- Increase energy supply
- Treat specific symptoms
- Avoid fasting
- Hydrate
- 3 small meals + 3 snacks a day
- Special care/caution with virus infections

- Exercise (exercise has been shown to increase mitochondrial function)
- Cofactors ("Mito cocktail")
- Medications (some psychotropic drugs have been shown to increase mitochondrial function) like amytriptiline, proton pump inhibitors

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